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EFFECT OF SINGLE AND REPEATED TETRACYCLINE  
ADMINISTRATION ON THE PHAGOCYTIC FUNCTION  
OF RETICULOENDOTHELIAL SYSTEMS

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EFFECT OF SINGLE AND REPEATED TETRACYCLINE  
ADMINISTRATION ON THE PHAGOCYTIC FUNCTION  
OF RETICULENDOTHELIAL SYSTEMS

[Following is the translation of an article by N. A. Kalinina and G. Ya. Kivman in the Russian-language journal Byulleten' Eksperimental'noy Biologii i Meditsini (Bulletin of Experimental Biology and Medicine), No 5, 1963, pages 84-87.]

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We previously established [ ] that single administration of chlortetracycline and oxytetracycline to white mice stimulates the absorptive function of the reticulo-endothelial system (RES) in several cases, depending on the dose of the preparation. Clinical use of tetracyclines is practically never restricted to single administration of the preparation; therefore it is important to know whether their stimulating effects on the RES [ ] retained upon repeated administration.

We studied the effect of single and repeated administration of chlortetracycline, tetracycline, and oxytetracycline on the absorptive function of mouse RES.

#### Experimental Methods

The state of the absorptive function of the RES under the effect of tetracyclines was determined by a microbiological method described earlier (1).

White mice weighing 18-20 grams were per os administered tetracycline administrations once in doses of 0.2, 0.5, 1.0, and

2.0 mg per animal (tetracycline in doses of 0.5, 1.0, and 2.0 mg). In 7 days the antibiotics were given again in doses stimulating RES during the single administration and last. In 30 minutes after administration of tetracyclines (in the repeated administration on the 7th day) the mice were intravenously given a suspension of aureous staphylococcus (strain No 209) and 5 minutes blood samples were taken for inoculation by means of decapitation. A measured quantity of blood was placed in petri dishes containing agar from a dry medium and in 36 hours colonies of staphylococci were counted. The animals of the control groups did not receive antibiotics. For standardization of the experimental conditions, experimental and control groups were apportioned for each batch of mice. Each group included 15-36 animals.

The material was treated statistically. The arithmetic mean, standard error, and confidence limits were established.

#### Experimental Results

Single administration of chlortetracycline to rats in doses of 0.5, 1.0, and 2.0 mg stimulated the absorptive function of the RES (1). Administration of antibiotics to the animals once in the dose of 0.2 mg was not reflected in the state of the RES.

Repeated administration of chlortetracycline in a dose of 2.0 mg led to inhibition of the RES and when 0.5 and 0.2 mg were administered on the 7th day the state of the absorptive function of the RES did not differ from that established for animals of the control groups (Table 1).

The single administration of tetracycline to the mice in dose of 2.0 mg stimulated the absorptive function of the RES; the preparation in doses of 0.5 and 1.0 mg had practically no effect on this system. Upon repeated administration of tetracycline in doses of 0.5, 1.0, and 2.0 mg indices of the state of the RES obtained at the end of the experiment did not differ from the control (Table 2).

Oxytetracycline in doses of 1.0 and 2.0 mg, when given once, had a stimulating effect on the RES. One-time administration of 0.2 and 0.5 mg of the preparation did not affect the state of the absorptive function of the reticulo-endothelial system of mice. Repeated administration of oxytetracycline in all cases give results not differing from the control groups (Table 3).

Therefore, upon repeated administration of tetracyclines, in contrast, followed the one-time administration, we cannot establish in a single case the stimulating effect of these antibiotics on the absorptive function of the RES. Repeated administration of chlortetracycline in the dose of 2.0 mg, which is a high therapeutic level, ultimately led even to a statistically

TABLE 1

The Effect of Single and Repeated Administration of Chlortetracycline on the Absorptive Function of Mouse RES

(a) Доза (в мг) и условия введения препарата	(b) Количество колоний (из 0,01 мл крови)
(c) 1.0 однократно . . . . .	74±10.1 (54.3-93.7)
(e) 2.0 " . . . . .	48± 5.7 (36.9-59.1)
(f) Контроль . . . . .	105± 6.3 (92.1-117.9)
(d) 0.5 однократно . . . . .	27± 4.6 (17.2-36.8)
(e) 0.5 повторно . . . . .	37± 5.8 (25.7-48.3)
(f) 2.0 " . . . . .	64±10.4 (43.7-84.3)
(d) Контроль . . . . .	41± 7.1 (26.5-55.5)
(c) 0.2 однократно . . . . .	47±12.1 (21.2-72.8)
(e) 0.2 повторно . . . . .	40± 8.5 (18.2-53.8)
(f) Контроль . . . . .	41±10.0 (18.7-63.3)

LEGEND: a) dose (in mg) and mode of administration of preparation; b) number of colonies (in 0.01 ml of blood); c) once; d) control; e) twice

significant increase in the index of staphylococcal inoculability in experiments compared with the controls. It is apparent that stimulation of the absorptive function of the RES noted in several cases during the single-time administration tetracyclines is quickly replaced by an inhibition of this function or by the lack of appreciable effect upon repeated administration of antibiotics. It is interesting to note that the repeated administration of tetracyclines to mice, not affecting the RES when given once (for chlortetracycline 0.2 mg, tetracycline -- 0.5 and 1.0 mg, and oxytetracycline (0.2 and 0.5 mg) in the cases of repeated administration also failed to stimulate the absorptive function of this system.

The data allows us to compare tetracyclines also as to their effect on the RES. Without danger of being in error, we can say that the more the index of staphylococcal inoculability in the experiment differs from the corresponding index in the control group, the more intensely does the preparation stimulate or inhibit the RES.

If from this point of view we compare the extent of the stimulating effect of tetracyclines on the RES, then we will find that it is most fully pronounced for chlortetracycline: it is shown when three doses are used (0.5, 1.0, and 2.0 mg); the ratio of inoculability indices in the control to the experimental

TABLE 2

**Effect of Single-Time and Repeated Administration of Tetracyclines on the Absorptive Function of Mouse RES**

(a) Доза (в мг) и условия введения препарата	(b) Количество колоний (из 0,01 мл. крови)
(с) 1,0 однократно . . . . .	134±16,7 (99,5÷163)
(e) 2,0      "	88±13,8 (59,5÷116,5)
(d) Контроль . . . . .	115±20,5 (72,6÷157,4)
(с) 0,5 однократно . . . . .	79±13,0 (49,6÷108,4)
(e) 0,5 повторно . . . . .	88±18,5 (49,2÷126,8)
1,0      "	81±18,0 (43,1÷118,9)
2,0      "	89±13,2 (61,1÷116,9)
(d) Контроль . . . . .	78±12,2 (52,2÷103,8)

LEGEND: a) dose (in mg) and mode of administration of preparation; b) number of colonies (per 0.1 ml of blood); c) once; d) control; e) repeated

TABLE 3

**Effect of Single and Repeated Administration of Oxytetracycline on the Absorptive Function of Mouse RES**

(a) Доза (в мг) и условия введения препарата	(b) Количество колоний (из 0,01 мл. крови)
(с) 1,0 однократно . . . . .	205±44,4 (114,0÷296,0)
(e) 2,0      "	185±35,6 (112,1÷257,9)
(d) Контроль . . . . .	298±43,7 (207,2÷388,8)
(с) 2,0 повторно . . . . .	75±12,3 (50,9÷99,1)
(d) Контроль . . . . .	72±11,0 (49,2÷94,8)
(с) 0,2 однократно . . . . .	55±12,0 (29,5÷80,5)
(e) 0,2 повторно . . . . .	66± 9,5 (45,9÷86,1)
(с) 0,5 однократно . . . . .	64±11,3 (43,9÷88,1)
(e) 0,5 повторно . . . . .	64± 7,1 (49,1÷78,9)
(d) Контроль . . . . .	43± 6,0 (40,5÷55,5)

LEGEND: a) dose (in mg) and mode of administration of the preparation; b) number of colonies (in 0.01 ml of blood); c) single-time; d) control; e) repeated

group is, respectively, 1.5, 1.4, and 2.2. The stimulating effect of oxytetracycline has been established for two doses (1.0 and 2.0 mg); the ratio of inoculability in the control to the experimental group is 1.4 and 1.6 [respectively].

The action of tetracycline is the least pronounced: it has been established for a single dose (2.0); the ratio of the index in the control to the experimental group is 1.3.

Only chlortetracycline has an inhibiting effect on the RES at the tetracycline doses used in the study. We established the lack of any effect on the RES in three instances for chlortetracycline and in five -- for tetracycline and oxytetracycline.

Thus, chlortetracycline acts the most intensely on the absorptive function of RES, followed by oxytetracycline, and finally tetracycline. Since according to our data the repeated administration of tetracyclines leads to the inhibition of the absorptive function of the RES or at best does not affect it, the clinical use of tetracycline is advisable.

#### Literature

1. Kalinina, N. A., Antibiotiki (Antibiotics), 1959, No. 4, page 88.
2. Ibid., Byulleten' eksperimental'noy biologii, 1963, No. 2, page 60.
3. Kivman, G. Ya., Kalinina, N. A., op. cit., 1962, No. 6, page 46.